Funding for Yale Cancer Answers is provided by Smilow Cancer Hospital.

Welcome to Yale Cancer Answers with your host doctor in Anees Chagpar.

Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week, it’s a conversation about using chemical tools to detect cancer causing proteins with doctor Stavroula Hatzios. Dr Hatzios is assistant professor of molecular, cellular and developmental biology and of chemistry at the Yale School of Medicine where Doctor Chagpar is a professor of Surgical oncology.

Maybe we can start off by you telling us a little bit more about yourself and what it is you do. My background is in chemistry and microbiology so not a traditional cancer biologist, but I use chemical tools to better understand infectious diseases and more specifically how microbes can contribute to cancer in humans. So in my training I started out by
researching infectious diseases,
particularly airborne pathogens.
Like Mycobacterium tuberculosis that causes human tuberculosis,
but then as a postdoc,
I switched to studying gastrointestinal pathogens,
principally vibrio cholera,
which is the bacterium that causes the diarrheal disease cholera.
And it was through my postdoctoral training that I began to engage in conversations with other scientists who recommended that I start applying some of the chemical tools and approaches that I was developing to study comparatively understudied microbes like Helicobacter pylori.
And that was really my entry point into the field of cancer microbiology and cancer microbiology really refers to an area of research that’s emerging where we’re looking at how microbes indigenous microbes in our bodies. Which comprise the microbiome, as well as infectious microbes that cause disease might contribute to the development of cancer in humans or alter outcomes of cancer therapies. So I begin researching Helicobacter pylori a little bit as a postdoc,
and that’s really been the focal point of my labs work. Trying to understand how this very important gastric or stomach pathogen causes cancer in a subset of infected humans, and what are the pathways the molecular events by which cancer develops and we use a lot of chemical approaches to sort of understand what those pathways are.

Yeah, so I was going to ask something along the same vein. Many people, when they think about Helicobacter pylori or H. Pylori, as it’s sometimes known we think about ulcers. We don’t really think about cancer. So can you talk a little bit more about the link between H. Pylori and cancer and how how you got started with that?

Absolutely yeah, H. Pylori is a fascinating, fascinating microbe. As you mentioned, it is primarily linked, at least in public knowledge, to peptic ulcers, stomach inflammation. But it’s also the leading risk factor for gastric cancer, which I think currently remains
the third leading cause of cancer related deaths worldwide. This is a microbe that’s found in half of the global population, and for most people it it doesn’t lead to cancer. It may actually be innocuous, meaning it may not do too much to the infected host, but a subset of those who carry the microbe as a normal part of their stomach microbiome will develop peptic ulcers and gastric inflammation, called gastritis. That’s roughly 10 to 15% of people who have H. Pylori and then a much smaller percentage. 1 to 3% typically go on to develop gastric cancer and this connection was only made a couple of decades ago by Robin Warren and Barry Marshall, who won the Nobel Prize in medicine in 2005 for this discovery that this microbe can cause peptic ulcers, gastric inflammation and ultimately cancer and in fact due to their work, H. Pylori is now the first microbe known to be a human carcinogen. So in individuals who have H.
the microbe can cause chronic inflammation of the gastric lining and overtime and some hosts. This can develop into gastric cancer. And what’s a major challenge for those of us in the field is trying to understand why it is that some individuals develop cancer and others do not. And that’s a really important question. The reason it’s so important is that typically if someone has H. Pylori, you can administer antibiotics to get rid of microbe, but these microbes have a way of evolving very rapidly and thus they evolve drug resistance, which limits the number of drugs that we have available to treat them. So if you just administer biotics to half the global population to rid them of H. Pylori, that may not be the best approach because you’ll fuel the rise of antibiotic resistance. And there’s also some emerging thought that H. Pylori may actually be beneficial to some portion of the population since.
People carry this microbe, usually from childhood, and it can help train the immune system similarly to how we think of other microbes that are found in our microbiome. So trying to understand whom should be treated with antibiotics and when who is at risk of developing cancer down the line. That’s a very important question, and that’s some of what our work is focused on understanding. So tell us more about that because that clearly is fascinating when you think about so much of the world’s population. Have this bacteria you know a reasonable proportion of them. Get gastritis and ulcers and are typically treated with as you say, antibiotics and acid reducing medications. But there is this subset who go on to get cancer. So what do we know about that population and why it is that they are more susceptible to developing malignancy? Great question. I think we don’t fully know and that’s something that a lot of research in the field is focused on. We have some indications as a field as to
what might be increasing the risk among certain individuals and those can range from geography to diet to genetic background, but there are challenges also in making some of those associations. So certainly there are certain parts of the world in which the incidence of H pylori associated gastric cancer is higher particular parts of South America? For example, there have been studies linking altitude to the risk of developing H. Pylori associated gastric cancer, as well as the amount of salt in the diet as well as iron levels. So various environmental factors are thought to increase risk and certainly genetic predisposition in some cases may play a role, although we don’t fully understand what those factors may be. A challenge there is that the microbe is found in such a large portion of the population. That it can be difficult to identify key factors that really predispose to the development of cancer and on the microbial side, which I haven’t really mentioned thus far. The Microbit itself has a very complex evolutionary history which in and of itself is super fascinating.
It’s thought to have evolved with humans since several thousand years ago, over 60,000 years. It’s been with humans and thus the phylogeny. Basically the evolutionary history. How this microbe has evolved. Can be used to trace migratory patterns of the human, the human race, and it’s really thought that the microbe evolves quite rapidly as well. Once it’s in a specific human host and thus it can be very difficult to assign specific microbial genetic patterns with cancer risk. Although there are, some important proteins and genes that the microbe carries which do correlate very strongly with cancer risk in some individuals. So, so how do we kind of move that forward? I mean when we think about people who you know present to their doctor with stomach pain and and ulcers and gastritis, they generally speaking will have an endoscopy and a small biopsy will be taken and sent to the lab and the lab will confirm that. Yes indeed they have H pylori. Is it, you know, given what you just mentioned,
is it possible for that lab instead of just saying yes, you have H. Pylori to look at the particular features of of that particular H. and say well, this particular brand of H. Pylori has an increased risk of you developing gastric cancer versus another brand of the same bacteria. Yes, I do think that that’s possible. It is possible to culture the microbes from human samples and assess at a genetic level if the microbe contains these. These risk factors, and I think that’s one possible approach. Practically speaking, it may be a bit challenging, but as we have more advances with regards to genome sequencing and PCR based methods that can help us identify these factors quickly, I think that’s one approach. I think what is maybe more important as we move forward in the field is trying to identify early risk factors because maybe one thing I haven’t mentioned is that gastric cancer tends to present quite later in life, so with with regards to H.
Pylori infection. As I mentioned, children usually are infected with the microbe when they’re very young. Typically we believe through household contacts with other family members who have the microbe. And it’s not until decades later that someone would present with gastric cancer. So this very long lag phase from the infection in childhood to the development of gastric cancer. And once it’s diagnosed, it can be pretty late stage. So that’s also challenging in terms of treatment. And so I think what’s needed are ways to assess much earlier. Whether or not someone is at risk and one way, as you mentioned, could be looking at the microbe and others. Others may be trying to identify. Host factors that may be indicative of infections that may be heading down the road towards cancer, and that’s what I think a lot of research in this area is focused on, including the work of my own lab,
is trying to identify effects that microbes may have on the host that could be translated into new diagnostic tests and indications of early cancer risk. So, tell us more about that in terms of the work that’s going on in your lab, sure. What we’re trying to do is excuse me, is trying to understand. How infection alters proteins in cells that are found in the stomach in a manner that may promote tumor growth. So how is it that the microbe interfaces with human proteins? How do they alter? How do those interactions alter the proteins behavior in a manner that could promote the development of cancer, so to break it down a bit when you have an infection, your body’s immune system will respond to try to clear the infection and that generally involves the recruitment of immune cells. And these immune cells will produce a lot of oxidants or free radicals. These are small molecules that are very reactive. They contain a lot of oxygen. They’re starved for electrons, so they react very readily with...
other molecules in your cells, and they can cause damage to cells.
Because of this intrinsic chemical reactivity.
And one of the major classes of biomolecules that can get damaged by these oxidants or proteins and proteins are super important because they do a lot of chemistry in ourselves.
They they generate energy, they help cells grow.
They help them divide.
They provide structure to cells.
They help mediate interactions between cells, and these are all very important processes that if they become dysregulated, so if they’re interrupted or inhibited, messed with in some way, they could lead to the development of cancer.
And So what we’re trying to understand is when you have an infection and all of these oxidants are produced by the immune system, some of those oxidants will damage proteins.
And when those proteins get damaged, do they alter some of these processes that could encourage cancer to form? If that’s the case in our data points, to indicates that that is.
Then can we identify you?
Some of these proteins as new
diagnostic markers of cancer risk?
So if these proteins are getting damaged early on, can we use them as indicators that cancer may be maybe more likely down the line?
Yeah, so I was just about to say, I mean, that sounds like just fascinating work and I’d really like to dig a little deeper into that. But first we have to take a short break for a medical minute. So please stay tuned to learn more information about research and to detecting cancer causing proteins with my guest doctor Stavroula Hatzios.

Funding for Yale Cancer Answers comes from Smilow Cancer Hospital hosting a Smilow shares cancer survivors series June 22nd and 29th. Register at yalecancercenter.org or e-mail cancer answers at yale.edu. Over 230,000 Americans will be diagnosed with lung cancer this year and in Connecticut alone there will be over 2700 new cases. More than 85% of lung cancer diagnosis are related to smoking and quitting even after decades of use can significantly reduce your risk of developing lung cancer each day.
Patients with lung cancer are surviving thanks to increased access to advanced therapies and specialized care, new treatment options and surgical techniques are giving. Lung cancer survivors more hope than they have ever had before. Clinical trials are currently underway at federally designated Comprehensive cancer centers, such as the battle two trial at Yale Cancer Center and Smilow Cancer Hospital to learn if a drug or combination of drugs based on personal biomarkers can help to control non small cell lung cancer. More information is available at yalecancercenter.org.
And we never really think about it necessarily as being associated with cancer. However, Savula tells us that it’s actually a leading cause of gastric cancer and the mechanism for that is something that she and her lab is working on discovering because not everybody who has H. Pylori gets gastric cancer. Thank goodness, but some people do. And so stavroula right before the break you were telling us that one of the potential mechanisms of this, if I understood correctly, is that with this H pylori infection your immune system starts to kind of act on that infection. It it kind of gets geared up as it would to any infection and starts manipulating some proteins and those proteins might actually signal cancer. Is that right?

Yes, that’s what we believe and what we’re investigating, and so we think that a lot of the inflammation that occurs during H. Pylori infection, which is accompanied by the production of oxidants, Those small molecules that are highly reactive, leads to changes in your cells, the proteins,
the DNA that helps nucleate cancer formation, and as you mentioned, we’re focusing on the proteins. How do those change in a way that may promote tumor growth? Our lab is using some advanced chemical tools that allow us to identify specific proteins and human gastric cells that get damaged or modified by these oxidants produced during H. Pylori infection, so we can basically canvas the whole cell with these chemical tools and say what proteins are you getting modified by these oxidants and then independently look at these proteins using biochemistry and some biology. Other very interesting tools in our toolkit to ask. What happens when these proteins are modified that may promote tumor growth, and for that we use a number of different model systems, both in the lab and using a number of other different systems to look at tumor growth as a result of these modifications to the proteins, the long term goal here is to identify modified proteins that could be used to diagnose cancer.
risk much earlier in an infection.
So you might imagine, as you mentioned previously, if someone presents at a clinic with an H. Pylori infection, maybe there could be a biopsy taken where we look specifically for proteins that we’ve identified in the lab. Promote tumor growth and see if those have been changed in a way that aligns with that outcome. And if you can detect those small molecular changes very early in an infection that may help improve outcomes on the patient side so that that’s an interesting theory. stavroula, but one of the things you mentioned before the break, which is true, is that there is this lag time right between when you get an infection when you have. Gastritis and when you may ultimately end up with gastric cancer, are there ways that we can manipulate these proteins or or reduce risk in some way? Once we identify these proteins, right? That is absolutely the goal. So not only could such proteins serve as indicators of cancer risk, but the nice thing about proteins, particularly a lot of
0:18:52.37 -> 0:18:53.72 the proteins that we study,
0:18:53.72 -> 0:18:56 is that a lot of them carry enzymatic.
0:18:56 -> 0:18:57.08 Function so there are enzymes.
0:18:57.08 -> 0:18:58.622 That means that they can perform
0:18:58.622 -> 0:18:59.92 different chemistry in the cell.
0:18:59.92 -> 0:19:02.284 They can perform chemical reactions and
0:19:02.284 -> 0:19:05.073 those are proteins that are really nicely
0:19:05.073 -> 0:19:07.365 targeted by small molecules by drugs.
0:19:07.37 -> 0:19:09.734 And thus if if these proteins
0:19:09.734 -> 0:19:12.319 that are involved in the infection
0:19:12.319 -> 0:19:14.629 response and down the line,
0:19:14.63 -> 0:19:16.195 increasing the risk of tumor
0:19:16.195 -> 0:19:18.17 growth can be targeted by drugs,
0:19:18.17 -> 0:19:20.336 then you also have the opportunity
0:19:20.336 -> 0:19:21.78 to develop new chemotherapeutics
0:19:21.838 -> 0:19:23.428 that could help actually treat
0:19:23.428 -> 0:19:25.018 cancers that result down the
0:19:25.074 -> 0:19:26.53 line from these infections.
0:19:26.53 -> 0:19:28.858 So not only are the proteins
0:19:28.858 -> 0:19:30.41 important as diagnostic indicators,
0:19:30.41 -> 0:19:32.312 but also carry the potential to
0:19:32.312 -> 0:19:34.479 be new drug targets for actually
0:19:34.479 -> 0:19:36.139 treating the cancer itself.
0:19:36.33 -> 0:19:38.227 Wouldn’t it be better if we were
0:19:38.227 -> 0:19:39.929 able to somehow manipulate these
0:19:39.929 -> 0:19:41.585 proteins to prevent cancer?
0:19:41.59 -> 0:19:43.198 Is that something that’s
0:19:43.198 -> 0:19:45.31 being looked at? Yes, I think
0:19:45.32 -> 0:19:47.39 we’re not quite there yet.
0:19:47.39 -> 0:19:49.124 We’re still at the early stages
0:19:49.124 -> 0:19:50.889 of trying to identify what these
proteins are and how they relate to the time course of cancer to the progression to cancer. From the point of infection. But yes, I think that there’s very much a possibility to intervene at a very early stage. If you do sort of a screen for such proteins at early points of infection, perhaps in an ideal scenario. In a case of a childhood infection, for example, if you see this sort of indication, then intervene at that point with these drugs that I mentioned might be down the line to kind of inhibit the activity that could lead to tumor development. You know you mentioned that half the world’s population. Actually carry this Helicobacter pylori in our stomachs and for the majority of us. Thank goodness we never have any problems. There’s a subset that get ulcers and a subset even smaller that goes on to get cancer. And I wonder whether. The latter subset who get cancer is a subset who actually get ulcers versus they can get cancer without having that intervening gastritis,
inflammation, kind of phase. In other words, if I have an asymptomatic infection with H. Pylori and I just carry this, but it never really bothers me. Am I at the same risk of getting gastric cancer? As a result of carrying that bug, as I would be if I not only carried H. Pylori but that H. Pylori went on to give me gastritis and ulcers and so on and so forth. And then I get gastric cancer. Do you understand my question? Yeah, I think so. And I should note again that I'm not a clinician, so this is certainly not my area of expertise. But I will say my understanding is that the latter holds true, so those individuals who do develop ulcers. You know, chronic inflammation. Gastritis are the subset that are at greater risk for developing cancer down the line and the the model in the field is that each pylori induces infection in some host induces this chronic inflammation and in some hosts and some humans who have the. The microbe overtime that leads to the development of this inflammation.
in the tissue and that process is what seeds the development of the cancer decades down the line as well. So it does correlate strongly with the incidence of inflammation and people who have each pylori and that makes so much sense because we’ve seen that in other cancers as well, where it really is. This inflammation, the damage to the tissues. This idea that you get inflammation? You get fibrosis. You get free radicals. You get an area of tissue which is not as well perfused. That can lead then to cancers and and so you know, presumably the tests that you’re developing to look at these these infections might be something that very easily could be done at the time that somebody presents for a biopsy. Diagnosing the H. Pylori to begin with when they have symptoms of gastritis. The next question is, you know if we know that it is the case that you know these gastric cancers tend to emerge in an area of inflammation and we can kind of see in your research and that
of others that the pathway seems to be these free radicals. These small molecules and damage to proteins and an inflammatory response, and so on and so forth. With your chemical toolbox where you're looking at these altered proteins. Have you looked at that in other cancers as well, and isn’t necessarily the case that these are always related to microbes? Or is it possible that some inflammation may be due to other causes, but that the end pathway, the end result in terms of the small molecules and the tissue damage and the protein damage, et cetera? With the inflammatory response is the same? That’s a great observation. And yes, I think it is very likely to be the case that a lot of these same protein damage pathways are are shared or are common amongst other cancers. We specifically, my lab specifically has not looked at other non infection associated cancers, but other labs have begun looking at this question and have certainly done it in other contexts as well, and I think that there will be an emerging picture of some proteins that get damaged.
By inflammation and oxidative stress and variety of contexts and that these may provide very important clues for the risk of cancer development, and I should also mention that one thing that we haven’t touched on is DNA damage, which is perhaps the more well known target of these oxidants that are generated during inflammation. And that’s something that is certainly very common across many different types of cancers resulting from infection or not. Oxidants can damage DNA, directly, and that can lead to mutations and instability of the genome that ultimately helps seed cancer formation as well. Yeah, the problem with that though, is that as you mentioned, the nice thing about proteins is that potentially you can do something about it. My perception is that that’s a little bit more difficult. I think you’re right. Yeah, I’m not familiar with specific work in that area, and I think it’s it’s a very important point that the benefit the
advantage to looking at proteins, which is still a very emerging area of research, is that you have the opportunity to intervene and actually do something about it. And they also have the added advantage of being both diagnostic indicators or providing some clues. What might be to come down the line, but also an opportunity to intervene through drugs? Small molecule approaches to help alter these outcomes? So I think for us, that’s why there’s such an exciting area of research, particularly as they relate to microbes. Yeah, you know, as you were talking about kind of these pathways and the way that H. Pylori works in terms of gastric cancer by you know, kind of getting the immune system to respond to it and then creating these. Small molecules and inflammation and so on. It. It made me think about other infections that we know also cause cancer, but that are not bacterial so we know H. Pylori is a is a little bacterium that lives in our stomachs. But we also know that many other cancers are caused by viruses. So thinking about hepatitis, for example,
0:27:09.81 - 0:27:12.225 the pathway seems to be very similar
0:27:14.449 - 0:27:16.794 Inflammation and fibrosis and free radicals and so on and so forth.
0:27:16.794 - 0:27:22.768 Is there a difference in terms
0:27:22.768 - 0:27:25.675 of how bacteria and viruses work
0:27:25.675 - 0:27:28.07 in terms of developing cancer?
0:27:28.07 - 0:27:31.112 And is it possible for your
0:27:31.112 - 0:27:33.42 research to potentially look at
0:27:33.42 - 0:27:35.7 virally mediated cancers as well?
0:27:36.9 - 0:27:39.455 Sure, I think that there are opportunities
0:27:39.455 - 0:27:41.911 to apply similar approaches to viral
0:27:41.911 - 0:27:44.509 infections that are associated with cancer.
0:27:44.51 - 0:27:48.092 And of course a lot of viruses have been
0:27:48.092 - 0:28:02.056 connected to very important malignancies,
0:27:51.04 - 0:27:52.868 HPV, human papilloma virus,
0:27:52.868 - 0:27:55.068 and cervical cancer.
0:27:55.068 - 0:27:56.19 That’s perhaps one of the
0:27:56.19 - 0:27:57.656 most well known connections,
0:27:57.656 - 0:27:59.136 but there are several others,
0:27:59.14 - 0:28:02.056 like hepatitis C, Epstein Barr virus,
0:28:02.06 - 0:28:04.358 and the link between viruses and
0:28:04.358 - 0:28:06.5 cancer has been explored for
0:28:06.5 - 0:28:09.992 quite a long time and a lot more is
0:28:09.992 - 0:28:13.367 known about how viruses can engage with
0:28:16.91 - 0:28:18.75 So some of the pathways may be similar,
0:28:18.75 - 0:28:20.502 but we think that they may also be
0:28:20.502 - 0:28:22.128 very distinct with regards to microbes,
0:28:22.13 - 0:28:23.41 but at the same time,
0:28:23.41 - 0:28:25.072 these approaches I think will be
very valuable for assessing viral infections and finding common pathways. Doctor Stavroula Hatzios is an assistant professor of molecular, cellular and developmental biology and of chemistry at the Yale School of Medicine. If you have questions, the address is canceranswers@yale.edu and past editions of the program are available in audio and written form at yalecancercenter.org. We hope you’ll join us next week to learn more about the fight against cancer here on Connecticut Public Radio. Funding for Yale Cancer Answers is provided by Smilow Cancer Hospital.